

REMARKS

I. Status of the Claims

Claims 1-5, 9-25 and 36-43 are pending in the application and stand rejected under 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejections Under 35 U.S.C. §103

A. **Radtke, Li and Davies**

Claims 1-5, 10-13, 19-25, 37-39 and 43 stand rejected over Radtke (U.S. Patent 6,521,226) in view of Li *et al.* (1995) and Davies *et al.* (1996). According to the examiner, Radtke provides all the necessary disclosure for recombinant expression of PON1, including PON1 Q and R, in humans, but fails to provide the motivation to do so in a subject exposed or at risk of OP toxicity. Li *et al.* is said to provide the missing motivation to use PON1 expression vectors such as a treatment or prevention of OP toxicity given that the reference allegedly teaches that "paraoxonase protects animals against organophosphate toxicity." Applicants traverse.

Applicants submit that Radke does indeed disclose information needed to provide for the recombinant expression of PON1 Q and R. However, as has already been acknowledged, this reference provides *no* motivation to use it for treating or preventing OP toxicity. Hence, the examiner has turned to Li *et al.* and Davies *et al.* As will be shown, these references are limited technically, and thus do not support the present rejection as argued by the examiner.

It is important to note that Li *et al.* isolated "PON," not PON1, from rabbits and it is highly uncertain what this composition contained. They certainly report no effort to characterize

the content of this composition. What *is* certain is that PON1 L and PON1 M were present, as well as PON1 Q and PON1 R, all in unknown distributions. It is also quite possible that PON2 and PON3 enzymes were present. So, from the teachings of Li, one of skill in the art could not possibly know *which* element of the composition was protecting the animals from chlorpyrifos toxicity. So, even with Radtke and Li combined, one still cannot link PON1 Q and/or R with protection from OP toxicity.

Turning to Davies *et al.*, this article does suggest a role for PON1 Q and R in protection from OP toxicity and differential potency of the PON1 Q and R isoenzymes in hydrolyzing different OPs. However, Davies' demonstration of substrate specificity for PON1 Q and R on serum samples tested *in vitro* was not sufficient to demonstrate that *boosting* PON1 Q and R isoenzyme concentrations *in vivo* would successfully protect against OP poisoning. The experiment of Davies *et al.* simply tested the hydrolytic activity of 92 serum samples of hispanic subjects to several OP chemicals *in vitro*. They did not test whether boosting the PON1 Q and R activity levels above what the subjects normally had would increase the protective effect. A genetic therapy depends on more factors than the gene activity for its success. For example, PON1 Q and R isoenzymes are bound to the high density lipoprotein (HDL) particle *in vivo*, and it was possible that the concentrations of HDL particles (PON1 binding capacity), or other physiologic factors, might have limited the hydrolytic effectiveness of the increases in production of the PON1 Q and R isoenzymes by the genetic therapy device. Many other potential influences could have limited the effects or increased the toxicity of boosting PON1 Q and R activity levels *in vivo*. None of these limitations could be discovered by simply measuring the differential hydrolysis rates of PON1 isoenzymes on serum samples *in vitro*.

In contrast, the present inventors were the first to demonstrate that substrate specificity was successfully produced by boosting PON1 Q and R levels *in vivo*, removing the uncertainty over the many possibly perturbing influences and demonstrating that no apparent toxic effects limited its usefulness. Without this information, one skilled in the art could not possibly have assured that a genetic therapy for OP toxicity could be successfully produced and offered. Likewise, Davies et al. state that “*We also show that the effect of the PON1 polymorphism is reversed for the hydrolysis of diazoxon, soman and especially sarin, thus changing the view of which PON1 isoform is considered to be protective.*” Abstract (emphasis added). Thus, it appears that Davies considered substrate specificity to be important, but determining such *in vitro* is not sufficient to predict what happens *in vivo*. This unpredictability is highlighted by Radtke, who taught that PON1 Q was the only important PON1 enzyme, albeit for atherosclerosis and not OP toxicity – an assertion now known to be false in the context of protecting against toxicity by some important OPs. Because the present inventors were the first to demonstrate the *in vivo* protective effects of PON1 Q/R recombinant therapy, including that PON1 R provided much better protection from chlorpyrifos than PON1 Q, they were the first to enable such treatments.

In sum, Radtke showed how to use PON1 Q and R in genetic therapy but held that only PON1 R was useful, Li showed that infusing an unspecified “PON” mixture imparts protection from OP’s *in vivo*, and Davies showed that higher PON1 Q and R confer different levels of protection to different OP’s, but these were innate levels that were not boosted. However, these papers articles did not address the question of whether *boosting both PON1 Q or R* will protect differentially from OP exposures *in vivo*. There simply were too many unknowns that had not been addressed, any of which could have made the concept fail. Only by performing the

experiment *in vivo* and showing that it worked could one claim to have possession of the reasonable predictability needed for obviousness, and that showing is missing from the prior art.

Thus, though the prior art may have pointed in the general direction of using PON1 to treat or protect from OP toxicity, it was far too speculative for those of skill in the art to consider it in any way predictable or straightforward that PON1Q and PON1R could be used this way. Indeed, had it been so straightforward, Radtke, who filed his application 2-3 years after the Davies *et al.* and Li *et al.* publications, would have undoubtedly included this embodiment in his patent. As such, reconsideration and withdrawal of the rejection, based on the foregoing, is therefore respectfully requested.

B. Radtke, Li, Davies and Scheffler

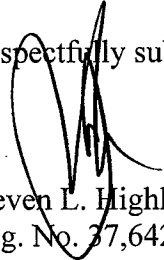
Claims 1, 9, 14-16, 21, 36 and 40-42 are rejected as obvious over Radtke, Li *et al.* and Davies *et al.* in view of Scheffler (U.S. Patent 5,721,118) under §103. The first three references are cited as above, and Scheffler is cited as teaching poly-A sequences and various promoters. Applicants traverse.

As discussed above, Radtke, Li and Davies do not render the present invention obvious. Scheffler, providing only structural elements for expression vectors, does not cure this defect, and as such, this rejection is improper as well. Reconsideration and withdrawal of this rejection is requested as well.

III. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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